Remarks

The claims of record have been rejected under 35 U.S.C. §112, §102 and §103(a). These rejections are respectfully traversed.

Claim Rejection – 35 U.S.C. § 112

The Examiner has rejected Claims 1-6, 8 and 11-16 under 35 U.S.C. §112, second paragraph for failing to comply with the written description requirement. Specifically, the Examiner has objected to the claim limitation "non-liposome multilamellar crystal non-polar phosphatidylcholine". This rejection is respectfully traversed.

The application at Page 5, ¶ [0013] specifies that:

> "the PPC-enriched phosphatidylcholine forms a bilayer enveloping the insulin to create the topical drug delivery composition, contributing to the stability of the active insulin molecules and enhancing penetration. Further, the stabilized insulin compositions . . . . may be in ***liquid crystal*** phase, with the PPC-enriched phosphatidylcholine loosely arranged in ***multilamellar*** fashion, with the polypeptide or macromolecule being bonded and entrapped within the lipid bilayers formed therein. This forms a loosely arranged, yet stable, PPC-enriched phosphatidylcholine-insulin complex that further increases penetration and delivery of the polypeptide or macromolecule to the dermal vasculature. "

Clearly the specification as filed defines subject matter which includes a ***multilamellar liquid crystal*** phosphatidylcholine. The ***multilamellar liquid crystal*** has ***bilayers*** entrapping the compound to be administered. Paragraph [0009] further specifies that the topical delivery compositions are ***non-polar***. Although the term "non-liposome" is not specifically referred to in the specification, a person of average skill in the art would know that a ***multilamellar liquid crystal*** is not a liposome. The addition

of the term “non-liposome” is not new matter. It is supported by the disclosure of the specification that the phosphatidylcholine is multilamellar..

The Examiner has questioned the use of the term “non-polar” noting that the carrier may be non-polar but questioning whether the phosphatidylcholine is non-polar. In response, claim 1 is amended to specify that the carrier is non-polar.

Withdrawal of the rejections under 35 U.S.C. §112, second paragraph is respectfully requested.

Claim Rejection – 35 USC § 102

The Examiner has rejected claim 1under 35 USC §102 as being anticipated by Hansen et al. (US 4,614,730). The applicant has previously asserted that the small amount of phosphatidylcholine disclosed by Hansen et al. is insufficient to entrap the insulin. The examiner disagreed with this argument stating “In the absence of evidence to the contrary, the amount disclosed by Hansen et al. is sufficient.”

In reasserting that the essentially homoepathic amount of phosphatidylcholine described by Hansen is insufficient to entrap the insulin, the applicant refers the Examiner to Claim 1 of Hansen (Column 8, lines 33-35) wherein he states “the insulin in solution being essentially **outside** any liposomes formed by said phospholipid.”

Clearly, the disclosure of Hansen is directed at a formulation that includes a small quantity of phospholipids for the purpose of creating a thin layer of phostatidylcholine at an air/water interface to stabilize insulin against interface polymerization (See Hansen, Col. 3, lines 45-Col. 4, line 8.)

Claim 1 of the present application is directed at a different formulation method used to create a non-liposome multilamellar liquid crystal for topical administration, not an aqueous insulin solution for parental administration (see Col. 8, line 9-10).

Accordingly, the claimed subject matter of claim 1 of this application is not anticipated by Hansen

Claim Rejection – 35 USC § 103

The Examiner has rejected claims 1-16, 8 and 11-16 under 35 USC §103 as unpatentable over Amselem et al. (U.S. Patent No. 5,662,932) in view of Hansen et al. (4,614,730) and Patel et al. (6,294,192) and, with respect to claims 2-6, 8, 15 and 16, in view of Chaiyawat et al. (U.S. Patent No.6,538,061) and Brieva (5,985,298).

In the Examiner's summary finding of prima facie obviousness (Page 9, line 4-6) he states "It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the insulin multilamellar liquid crystal phosphateidylcholine preparation of Amselem et al. with a combination of PEG 200 and PEG 400 as suggested by Patel to produce the instantly claimed invention.

The applicant asserts that the carrier described by Amselem in US 5,662,932 is inherently and structurally different from the carrier described within the instant invention. An accurate reading of Amselem (Column 2, lines 43-46) is that "the core is composed of a lipid which in the bulk form is in a solid or liquid crystalline phase." The carrier, referred to by Amselem as an emulsome, has the characteristics of both liposomes and emulsions. These emulsomes have an "internal solid lipid core" (Column 2, line 52). Amselen's structure is "stable solid fat nanoemulsions or emulsomes" (Column 2, lines 59-60) which have "solid lipid compositions as the core." (Column 2, lines 64-65). Thus the carrier claimed by Amselem is solid.

Patel et al. teach a pharmaceutical composition to topical drug delivery of therapeutic agents comprised of at least one hydrophobic and one hydrophilic surfactant. Patel does not expressly teach on phospholipid carrier structures which are, in fact, ambiphilic. Patel, in teaching on the use of two components, one hydrophilic and one hydrophobic, teaches away from the use of ambiphils such as those described in the present invention. Nowhere within U.S. Patent No. 6,294,192 does Patel describe the hydrophobic surfactant as a lubricant, as the examiner alleges. Patel does not mention the combination of polyethylene glycols (PEGS) with PPC-enriched phosphatidylcholi-

nes to produce the multilamellar structures described within the instant invention. Therefore, Amselem et al., describing a solid ordered "emulsome", in combination with the teaching of Patel do not together make the present invention obvious to one of ordinary skill in the art.

Chaiyawat et al. teach the use of silicone fluids such as dimethicone as carriers of drugs for topical administration. Chaiyawat does not describe these silicone fluids as lubricants but as the carriers (i.e. solvents) for the drugs themselves. As such there would be no motivation for one of average skill in the art to combine the teachings of Chaiyawat with those of Amselem to arrive at the present invention.

Brieva et al. teach cosmetic compositions comprised of non-volatile silicones, such as Dow 190, for improved long lasting adherence to the skin of cosmetics. The present invention is not directed toward cosmetics. Neither Brieva nor Chaiyawat mention the use of phosphatidylcholines to produce the multilamellar structures described within the instant invention.

Accordingly, Amselem et al., describing a solid ordered "emulsome", in combination with the teaching of Patel, or Chaiyawat and Brieva, or Hansen, do not make the present invention obvious to one of ordinary skill in the art. The nature of the teachings of these various references tend to be divergent rather than convergent and therefore one of ordinary skill in the art would not have been motivated to make these divergent combinations with any reasonable expectation of success in producing the instantly claimed invention.

Having described an entirely different structure to the carrier, one of average skill in the art would have no rational nor motivation to use to modify this carrier by addition of PEG 200 and PEG 400 with the expectation of arriving at the instantly claimed invention. In addition, one would have no motivation nor rational that the use and addition of

lubricious silicone fluids and/or siloxylated polyethers such as DOW 190 and/or preservatives, when combined with the teachings of Amselem would bring one to the presently described invention.

The present invention provides for a method of formulating an insulin composition within a phosphatidylcholine carrier, wherein said insulin is stabilized at room temperature. Neither the disclosed invention nor its benefits are disclosed or suggested by the combination of references. It is submitted that the presently claimed invention is patentable over Hansen et al. and over Amselem et al. in view of Patel, Hansen, Chaiyawat and Brieva, and issuance of a Notice of Allowance is respectfully requested.

Respectfully submitted,

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